Appendix A

PROCESS FOR MAKING BOC-PROTECTED 3-AMINOHYDANTOINS/THIOHYDANTOINS AND 3-AMINODIHYDROURACILS/DIHYDROTHIOURACILS

This application is a 371 of PCT/US00/27503 filed October 5, 2000 which claims the benefit of Provisional Application No. 60/158,660 filed October 8, 1999.

Technical Field

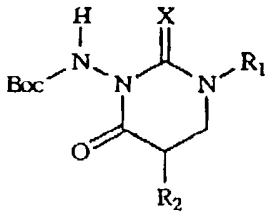
The present invention is directed to a process for the efficient solution and solid-phase synthesis of Boc-protected 3-aminohydantoins/thiohydantoins and 3-aminodihydrouracils/dihydrothiouracils.

Background of the Invention

The present invention is directed to a novel process for synthesizing Boc-protected 3-aminohydantoins, 3-aminodihydrouracils, and their thio-substituted counterparts using a one-pot solution-phase or solid-phase process. 3-aminohydantoin and 3-aminodihydrouracil derivatives are useful in both the pharmaceutical and agrochemical industries. For example, compounds containing the 3-aminohydantoin or 3-aminodihydrouracil nucleus are useful as anticonvulsant agents, antibacterial agents, metalloprotease inhibitors, diuretic agents, and pesticides.

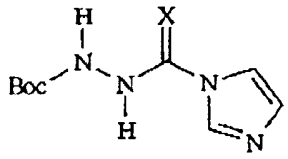
Synthetic routes for the preparation of 3-aminohydantoin derivatives are disclosed in the following references: Kiec-Kononowicz, K.; Zejc, A.; Byrtus, H. *Pol. J. Chem.* **1984**, *58*, 585. Lange, J. *et al. Polish Patent*, PL 123138 B1, April 30, **1984**. Wright, G. C.; Michels, J. G.; Spencer, C. F. *J. Med. Chem.* **1969**, *12*, 379-381. Bernard, L. *et al. French Patent*, 2000801, January 24, **1969**. Kobayashi, N. et al. *Japanese Patent*, 09176131 A2, July 8, **1997**. Taub, W. *U.S. Patent* 2767193, **1956**. *Chem. Abstr.*, **1957**, *51*, 5811. Szczepanski, H.; Kristinsson, H.; Maienfish, P.; Ehrenfreund, J. WO 95/18123, **1995**. Lindemann, A.; Khan, N. H.; Hofmann, K. *J. Am. Chem. Soc.*, **1952**, *74*, 476-479. Gante, J.; Lautsch, W. *Chem. Ber.*, **1964**, *97*, 994. Schlogl, K.; Derkosch, J.; Korger, G. C. *Monatsh. Chem.* **1954**, *85*, 607. Schlogl, K.; Korger, G. *Monatsh. Chem.* **1951**, *82*, 799. Davidson, J. S. *J. Chem. Soc.* **1964**, 4646-4647. Gillis, B. T.; Dain, J. G. *J. Heterocyclic Chem.* **1971**, *8*, 339-339. Wildonger, R. A.; Winstead, M. B. *J. Heterocyclic Chem.* **1967**, *4*, 981-982. Lalezari, I. *J. Heterocyclic Chem.* **1985**, *22*, 741-743. Saegusa, Y.; Harada, S.; Nakamura, S. *J. Heterocyclic Chem.* **1990**, *27*, 739-742. Milcent, R.; Akhnazarian, A.; Lensen, N. *J. Heterocyclic Chem.* **1996**, *33*, 1829-1833. Ragab, F. A.; Eid, N. M.; El-Tawab, H. A. *Pharmazie* **1997**, *52* (12), 926-929. Yoon, J; Cho, C-W; Han; H; Janda, K. D. *Chem. Comm.* **1998**, 2703-2704. However, in general the synthetic routes disclosed above involve multiple steps, require harsh reaction conditions, and/or produce relatively low yields.

14. (Currently Amended) A method for making a 3-aminodihydrouracil or 3-aminodihydrothiouracil having the formula:

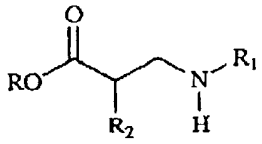


wherein X is oxygen or sulfur, R_1 is hydrogen, alkyl, a heterocyclic ring, an aromatic ring, or a heteroaromatic ring; R_2 is hydrogen, alkyl, a heterocyclic ring, an aromatic ring, or a heteroaromatic ring; or R_1 and the member carbon atom adjacent to the carbon atom containing R_2 can be taken together to form a ring system; said ring system being ~~carboxyxlic~~ carbocyclic ring, heterocyclic ring or heteroaromatic ring; said method comprising the steps of:

a) reacting a hydrazine compound having the formula:



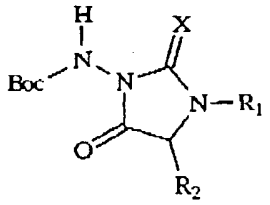
with an amino acid ester having the formula:



R is alkyl, carbocyclic ring, heterocyclic ring, aromatic ring, or heteroaromatic ring, to form a reaction mixture; and

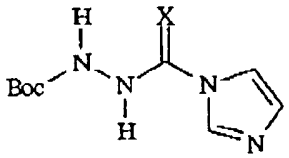
b) heating said reaction mixture to form said 3-aminodihydrouracil or 3-aminodihydrothiouracil.

26. (Currently amended) A method for making a hydantoin or thiohydantoin having the formula:

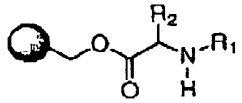


wherein X is oxygen or sulfur, R_1 is hydrogen, alkyl, a heterocyclic ring, an aromatic ring, or a heteroaromatic ring; R_2 is hydrogen, alkyl, a heterocyclic ring, an aromatic ring, or a heteroaromatic ring; or R_1 and R_2 can be taken together to form a ~~fused~~ carbocyclic ring, heterocyclic ring, ~~a fused aromatic ring,~~ or ~~a fused~~ heteroaromatic ring ~~with the hydantoin or thiohydantoin ring~~; said method comprising the steps of:

a) reacting a hydrazine compound having the formula:



with a resin-bound amino acid ester having the formula:

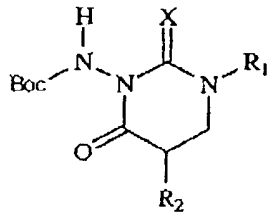


wherein the symbol:

signifies a Merrifield resin, hydroxymethyl, resin, Wang resin, or PEG resin; to form a reaction mixture; and

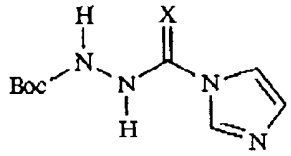
b) heating said reaction mixture to form said hydantoin or thiohydantoin.

27. (Currently Amended) A method for making a 3-aminodihydrouracil or 3-aminodihydrothiouracil having the formula:

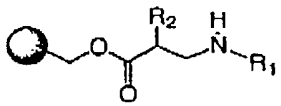


wherein X is oxygen or sulfur, R_1 is hydrogen, alkyl, a heterocyclic ring, an aromatic ring, or a heteroaromatic ring; R_2 is hydrogen, alkyl, a heterocyclic ring, an aromatic ring, or a heteroaromatic ring; or R_1 and the member carbon atom adjacent to the carbon atom containing R_2 can be taken together to form a ~~fused~~ carbocyclic ring, heterocyclic ring, ~~a fused aromatic ring,~~ or ~~a fused~~ heteroaromatic ring ~~with the 3-aminodihydrouracil or 3-aminodihydrothiouracil ring~~; said method comprising the steps of:

a) reacting a hydrazine compound having the formula:



with an amino acid ester having the formula:



wherein the symbol:

signifies a Merrifield resin, hydroxymethyl, resin, Wang resin, or PEG resin; to form a reaction mixture; and

b) heating said reaction mixture to form said 3-aminodihydrouracil or 3-aminodihydrothiouracil.